REMARKS

Entry of this amendment and reconsideration of this application are respectfully requested.

The undersigned gratefully acknowledges the courtesies extended by the Examiner during the telephone interview of April 16, 2009, and agrees with the Examiner's Interview Summary.

Claims 18-22 and 26-44 were rejected under 35 U.S.C. §103(a) for allegedly being unpatentable over the combination of Vinegar in view of Hunter or Silvestrini, both in view of Mizuno and Ikehara. Applicants respectfully traverse.

Vinegar teaches 3-deazaadenosine as an agent suitable for treating inflammation. However, Vinegar fails to disclose that this compound is suitable for coating stents and therefore does not teach a stent coated with 3-deazaadenosine or an analogue thereof. Furthermore, this reference does not teach a method of treating or preventing stenting-associated symptoms as claimed in present claim 21.

Silvestrini discloses a stent for implanting in the body lumen. Furthermore, according to Silvestrini, a stent may act as a sustained release applicator generally for anti-inflammatory drugs. However, Silvestrini does not disclose 3-deazaadenosine or an analogue thereof and does not teach a stent coated with said compounds and further does not teach a method for suppressing/avoiding undesired side-effects following stenting. Furthermore, Silvestrini fails to provide any hint as to covalent binding of drugs to a stent.

Hunter discloses stents encoated with a composition comprising anti-angiogenic compounds and anti-inflammatories. Hunter, however, does not give any hint or suggestion as to coating a stent with 3-deazaadenosine or an analogue thereof for treating and/or preventing stenting side-effects. Furthermore, Hunter does not give any hint or suggestion of the covalent binding of drugs to a stent.

Newly cited references Mizuno et al. and Ikehara each disclose 3-deazaadenosine derivatives but do not give any hint or suggestion as to the subject matter of the presently claimed invention.

It was an object of the present invention to inhibit and/or prevent undesired stenting-associated side-effects. The present inventor surprisingly discovered that typical stent-associated side-effects do not occur when stent implants are coated with 3-deazaadenosine or an analogue thereof. Characteristic stenting-associated side-effects are include vasculopathies as restenosis, reperfusion injury, infectious coronary syndrome, inflammatory coronary syndrome and dilated cardio-myopathy.

The pathophysiology of stenting-associated conditions like restenosis is multifactorial and comprises inflammation, smooth muscle cell migration and proliferation and extracellular matrix formation, all mediated by distinct molecular pathways. Molecular reasons for these vasculopathies are, amongst others, the expression of endothelial cell adhesion molecules, as for example VCAM-1 and ICAM-2 after stent implantation. As a result, apart from inflammatory reactions, especially proliferation processes are activated in the affected vascular walls, leading to neoplastic tissue growth. This neoplastic tissue extends into the lumen of the blood vessel, leading to a stenosis of the vessel.

Therefore, the ideal drug to prevent side-effects of stent implantation like restenosis must have various effects, namely:

1. an anti-inflammatory effect,
2. an anti-proliferative and anti-migratory effect on smooth muscle cells, and
3. must allow re-endothelialization.

The inventor of the presently claimed invention discovered that 3-deazaadenosine or an analogue thereof is, apart from its already known anti-inflammatory effect (inhibition of the infiltration of monocytes into vascular walls), additionally, and above all, active in the inhibition of the expression of endothelial cellular adhesion molecules. It is exactly this inhibition which successfully prevents the proliferation processes induced by stenting, i.e. activation of cell division in the endothelial layers of the blood vessel and, consequently, vascular stenosis.

The aforementioned physiological reactions to stenting are especially effectively inhibited when stents are coated or covalently coated, respectively, with 3-deazaadenosine or an analogue thereof.

The inventor of the present invention has, for the first time, proved the inhibiting effect of 3-deazaadenosine or an analogue thereof with regard to physiological (proliferative) processes associated with stenting as well as the efficacy of said compounds on stents coated therewith. The inventor also discovered, for the first time, that 3-deazaadenosine inhibits the proliferation of smooth muscle cells and the cell cycle via an interaction with the Ras signal cascade.

The cited references neither provide any hint or suggestion as to the anti-proliferative effect of 3-deazaadenosine or an analogue thereof, which is essential for the effective prevention of stenting-associated side-effects, nor to the coating of stents with these compounds.

Vinegar only discloses that 3-deazaadenosine has an anti-inflammatory effect. Vinegar is based on a patent application filed on April 25, 1980. The Examiner is invited to note that stenting associated disorders such as in-stent stenosis were not known at that time, since the first stents had primarily been implanted at the end of the 1980's. A connection between 3-deazaadenosine disclosed herein and physiological reactions associated with stenting could not, therefore be obvious from Vinegar. At the priority date a person skilled in the art trying to solve the problem of the present invention would have had no motivation to consider Vinegar, since there is neither described the anti-proliferative effect of 3-deazaadenosine, nor the coating of stents with this compound.

Furthermore, a combination of Vinegar with either of Silvestrini or Hunter does not render the subject matter of the present invention obvious. Silvestrini and Hunter disclose stents which may be coated with anti-inflammatory agents. They do not, however, provide any hint or suggestion regarding stents coated with compounds having the pharmacological profile of 3-deazaadenosine. More specifically, the cited references do not, alone either in combination, provide any hint as to stents covered with an agent inhibiting specific physiological processes induced by stenting, i.e. inflammation, cellular migration and proliferation and extracellular matrix formation in vascular walls.

A person skilled in the art having knowledge of the cited state of the art and the references cited below would rather have been led away from the present invention, since it had

been known from the art that anti-inflammatory drugs were not suitable to inhibit the proliferation of smooth muscle cells and, thus, stenting-induced side-effects as for example restenosis. For example site specific drug delivery of dexamethasone to porcine coronary artery wall had no effect in treating restenosis in a study published by Park and Linkoff (Park SH, Lincoff AM, Sem Interv Cardiol 1998;3:191-195). In another study published by Wang et al. (Wang L. et al., Cor Artery Dis 2005;16:237-243), stent mediated methylprednisolone delivery reduces macrophage content, but did not reduce proliferation of smooth muscle cells. It is exactly such proliferation, however, that is to be inhibited in the treatment of undesired stenting-induced side-effects.

The reference cited by the Examiner fail to provide any hint regarding stenting-induced proliferation in endothelial tissue causing undesired side-effects which are to be avoided, nor to the fact that stents coated with 3-deazaadenosine are effective in the treatment of these stenting induced side-effects. Starting from Vinegar, Silvestrini and Hunter, there was, consequently, no reason to coat stents with 3-deazaadenosine or a derivative thereof. The subject matter of the present invention is not, therefore, rendered obvious by Vinegar in view of Silvestrini and/or Hunter.

In summary, a person skilled in the art with the goal of effectively inhibiting stent-associated side-effects would not have been motivated to combine Vinegar, Silvestrini and Hunter, since, on the one hand, he did not have the knowledge that inflammatory reactions proliferative processes should be inhibited to prevent of detrimental stent-associated side-effects. On the other hand, the cited state of the art does not disclose or suggest that proliferative processes in the vascular walls can successfully be inhibited by 3-deazaadenosine. Only an impermissible hindsight view would lead a person of skill in the art to stents coated with 3-deazaadenosine.

Finally, the cited references do disclose the subject matter of present claim 20, since they do not give any hint or suggestions as to the advantageous effect of stents covalently coated with 3-deazaadenosine.

In view of the foregoing, allowance is respectfully requested.

If any fees are, authorization is given to charge deposit account no. 50-0624.

Respectfully submitted,

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